



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| (51) International Patent Classification <sup>6</sup> :<br><b>C12N 15/12, C07K 14/705, 16/28, G01N 33/68, C07F 9/30, C12N 15/11, A01K 67/027</b>   |                         | A1   | (11) International Publication Number: <b>WO 97/46675</b><br>(43) International Publication Date: 11 December 1997 (11.12.97) |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
|--|-------------------------|--|---|-------------------|-------------------------|-------------------------|-------------------|---|---|-------------------|----|----|------------------|----|----|------------------|----|----|------------------|----|----|------------------|-----|-----|------------------|-----|-----|------------------|-----|-----|------------------|-----|-----|
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| (30) Priority Data:<br>08/655,716 30 May 1996 (30.05.96) US<br>08/756,091 22 November 1996 (22.11.96) US   |                         | (81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| (60) Parent Application or Grant<br>(63) Related by Continuation<br>US 08/756,091 (CIP)<br>Filed on 22 November 1996 (22.11.96)  |                         | Published<br>With international search report.   |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
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| (54) Title: METABOTROPIC GABA[B] RECEPTORS, RECEPTOR-SPECIFIC LIGANDS AND THEIR USES   |                         |  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| <table border="1"> <caption>Data points estimated from the graph</caption> <thead> <tr> <th>Concentration (M)</th> <th>% Inhibition (Series 1)</th> <th>% Inhibition (Series 2)</th> </tr> </thead> <tbody> <tr><td>10<sup>-11</sup></td><td>0</td><td>0</td></tr> <tr><td>10<sup>-10</sup></td><td>10</td><td>10</td></tr> <tr><td>10<sup>-9</sup></td><td>30</td><td>30</td></tr> <tr><td>10<sup>-8</sup></td><td>60</td><td>60</td></tr> <tr><td>10<sup>-7</sup></td><td>90</td><td>90</td></tr> <tr><td>10<sup>-6</sup></td><td>100</td><td>100</td></tr> <tr><td>10<sup>-5</sup></td><td>100</td><td>100</td></tr> <tr><td>10<sup>-4</sup></td><td>100</td><td>100</td></tr> <tr><td>10<sup>-3</sup></td><td>100</td><td>100</td></tr> </tbody> </table>  |                         |  |   | Concentration (M) | % Inhibition (Series 1) | % Inhibition (Series 2) | 10 <sup>-11</sup> | 0 | 0 | 10 <sup>-10</sup> | 10 | 10 | 10 <sup>-9</sup> | 30 | 30 | 10 <sup>-8</sup> | 60 | 60 | 10 <sup>-7</sup> | 90 | 90 | 10 <sup>-6</sup> | 100 | 100 | 10 <sup>-5</sup> | 100 | 100 | 10 <sup>-4</sup> | 100 | 100 | 10 <sup>-3</sup> | 100 | 100 |
| Concentration (M)  | % Inhibition (Series 1) | % Inhibition (Series 2)  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-11</sup>  | 0                       | 0  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-10</sup>  | 10                      | 10   |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-9</sup>   | 30                      | 30   |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-8</sup>   | 60                      | 60   |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-7</sup>   | 90                      | 90   |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-6</sup>   | 100                     | 100  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-5</sup>   | 100                     | 100  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-4</sup>   | 100                     | 100  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| 10 <sup>-3</sup>   | 100                     | 100  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| (57) Abstract.   |                         |  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |
| <p>The present invention provides purified GABA<sub>B</sub> receptors and receptor proteins derived from rat and human sources, as well as nucleic acids which encode such proteins. The proteins and nucleic acids of the invention share significant homology with the GABA<sub>B</sub> receptor and the DNA encoding it as specifically disclosed herein. The invention moreover provides methods for isolating other members of the GABA<sub>B</sub> receptor family using DNA cloning technology and probes derived from the sequences provided herein, as well as novel members of the GABA<sub>B</sub> receptor family isolated by such methods. Furthermore, the invention relates to the use of GABA<sub>B</sub> receptors and receptor proteins and cells transformed with a gene encoding a GABA<sub>B</sub> receptor protein in a method for identifying and characterising compounds which modulate the activity of the GABA<sub>B</sub> receptor, such as GABA<sub>B</sub> receptor agonists and antagonists, which may be useful as pharmacological agents for the treatment of disorders associated with the central and peripheral nervous systems.</p> |                         |  |   |                   |                         |                         |                   |   |   |                   |    |    |                  |    |    |                  |    |    |                  |    |    |                  |     |     |                  |     |     |                  |     |     |                  |     |     |